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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,073	BRYAN, PHILIP N.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *18-45 and 50-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship 7 March 2006 to priority under 35 U.S.C. § 119 of the 6 August 2003 filing date of the US provisional application No. 60/494,032, and its successor International patent application PCT/US04/21049 filed 29 June 2004, is hereby acknowledged.

Preliminary Amendment

Applicant's Preliminary Amendments filed with the application on 3 February 2006, adding the new claims 12 and 46-61 and amending page 1 of the specification, have been entered. Claims 1-61 remain in the application.

Election/Restrictions

Applicant's (i) election without traverse of the invention of Group 1, comprising claims 1-17 and 46-49, and (ii) further election within that Group of species of methods practiced with, or products comprising, the subtilisin species S189, S190, S196, S197, S198, S199, or S201, in the reply filed on 18 January 2008 are hereby acknowledged. Claims 18-45 and 50-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 18 January 2008, accordingly claims 1-17 and 46-49 are initially examined herein to the extent they describe elected polynucleotides encoding fusion polypeptides comprising prodomains cleavable by at least one of the subtilisin species S189, S190, S196, S197, S198, S199, or S201, each of which is a variant of the native subtilisin BPN' the precursor of which comprises SEQ IDs NOs:1-3, as well as recombinant methods of making utilizing the elected polynucleotides and their encoded products. Currently, none of the elected claims requires any particular species of subtilisin BPN' variant.

Objections to the Disclosure and the Claims: Informalities

The disclosure is objected to because of the following informalities:

The designation "Δ", a frequently-used form of designating a deletion of amino acids, is absent before the term "75-84" at page 2, line 21.

Claim 1 lacks an indefinite article before the second occurrence of "coding sequence".

Claim 1 lacks the definite article before the term "corresponding protease".

Claim 4 lacks spaces and punctuation between words and terms at line 4 of the claim.

Claim 6 lacks punctuation between "Y" and "H" at line 3 of the claim.

Claim 10 inappropriately states "variations of amino acid residues" because the clear intent of the claim is not modification of each of the nine different amino acids present in a nonapeptide but a selection among discrete sets of amino acids at two positions within the nonapeptide sequence.

Claims 11 and 16 have the term "alpha" misspelled before the term "glucosidases".

Claims 11 and 16 have the term "membrane" misspelled before the term "proteins".

Claim 12 inappropriately states "encoding for" because the preposition is superfluous.

Claim 46 lacks an indefinite article before the second occurrence "coding sequence".

Claim 49 lacks punctuation between "V" and "or" at line 2 of the claim.

Appropriate correction is required.

Objection to the Disclosure: Essential Material

The term "pr8" first appears in the specification in the description of Figure 7 at page 11, accompanied by the tetrapeptide indication **"FKAM"**, and is next referenced in Examples 1-3, where it appears to be intended to refer to a particular prodomain. Reference to a successor prodomain structure, pr58, first appears in the discussion of Example 3. However, no structure of a "pr8" prodomain, and no structure of the successor pr58 prodomain appear to have been provided in the specification. The specification establishes o relationship between SEQ ID NO:2 of the sequence disclosure and either of a "pr8" or a "pr58". Applicant is invited to clarify, or to identify, any disclosure of either structure in the specification, or in a US Patent cited in the specification which might permit the incorporation of (a) structure(s) by reference.

Objection to the Specification: Lack of Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: (i) a nonapeptide formula appears in claim 10 as well as at page 6, line 21, and at page 25, line 6, of the specification, (ii) a hexapeptide appears at page 20, line 33, of the specification, and (iii) different pentapeptides appear in the final paragraph at page 21, as well as at page 22, of the specification. Each sequence is subject to the Sequence Rules but none are identified by a sequence identification number or appear in the Sequence Disclosure. Applicant's attention is directed to 37 CFR 1.821, which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded

by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time that reference is made in the specification or in the claims, e.g., claim 10, to a peptide larger than a tetramer, it should be accompanied by a sequence identifier stating "SEQ ID NO:N", where N is an integer, and the sequence and sequence identifier must be included in the Sequence Disclosure in the specification. In order to expedite prosecution, and in response to this communication, Applicant is required to amend the specification to provide a revised Sequence Disclosure in both computer-readable and printed forms, and to submit a Statement of Sameness attesting to the identity of both, where the revised Sequence Listing includes the hexapeptide sequence, the pentapeptide sequences and the nonapeptide sequence, either as six separate nonapeptide sequences or a single nonapeptide sequence set forth as a formula where "Xaa" appears at the two positions where different amino acids are available and each "Xaa" is further defined within the entry for its sequence identifier

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 46-49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 and 46-49 are rejected as being incomplete for omitting an essential structural cooperative relationship of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The recitation of "operatively linked" in each of the independent claims 1, 7, 12, and 46 is construed to describe the formation of a peptide bond between the encoded elements in the process of translation of an RNA transcript arising from the DNA sequence of a "nucleic acid construct" and claim 13 omits a recitation of even this kind of relationship. All claims omit a necessary structural cooperative relationship between the two fusion partners in an encoded fusion polypeptide: their orientation. The specification discloses (i) that the prodomain is amino-proximal with respect to a necessarily carboxyl-terminal "protein of interest, and (ii) the presence of a peptide bond directly between the two fusion partners. In the absence of a description of such orientation there is no basis for distinguishing between a prodomain and a "protein of interest" because the action of a "corresponding protease" is superfluous without the necessary structural cooperative relationship. Claims 2-6, 8-11, 14-17, and 47-49 are all included in this rejection because they fail to supply the necessary structural cooperative relationship absent from the descriptions of the claims from which they depend.

Claim 1 is independently indefinite in failing to provide a basis for distinguishing between an "increased affinity" for, and a "correspondence" between, a fusion partner and a protease or variant of a protease because both "increased affinity" and "correspondence" are (i) relative terms as well as (ii) functional terms but the independent claims provide no structural basis for either "affinity" or "correspondence" that might permit the artisan and the public seeking to ascertain the metes and bounds of the intended subject matter to determine which is important to, or the extent of the relative contribution of either to, the relationship between a prodomain in a fusion protein and an external protease. Claims 2-4 are included in this rejection because, unlike claims 5 and 6 which provide a definite basis for "correspondence" with respect to a particular class of proteases, they fail to resolve the indefinite description of claim 1.

Claim 10 is indefinite in reciting an intended use "to be used" together with a relative term, "cognate" without an indication of the intended cognition, thus the artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot determine the basis of both the use and cognition to which the structure is directed, particularly where the structural relationship of the nonapeptide is not established in the claim.

Claim 46 is indefinite because the recitation of the claim establishes no distinction between the two fusion partners of the fusion protein that might permit the artisan and the public seeking to ascertain the metes and bounds of the intended subject matter to determine which of them "generates affinity" for a protease, or whether or not both are required as fused to "generate[s] affinity".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 46, and 47 are rejected under 35 USC § 102(e) as being anticipated by Van Rooijen et al., US 2003/0166162, made of record herewith, who disclose the preparation of polynucleotides that encode fusion polypeptides comprising any one of several modified chymosin prodomains fused directly to the amino terminus of any one of several desired, carboxyl-proximal, polypeptide fusion partners – hormones – wherein the modified prodomains

present in recombinantly expressed fusion polypeptides are disclosed to have an improved affinity for chymosin as shown by increased yields of cleaved fusion partner achieved, relative to that achieved with an unmodified chymosin prodomain, in the 16 hour, room temperature incubations with added chymosin in Table 2, paragraph 0166, anticipating the subject matter of claim 1 herein. The prodomain alterations of Van Rooijen et al. are also considered to meet the less specific functional phrase "generates affinity" of claim 46 in view of the improved affinity for chymosin demonstrated by increased yields of cleaved fusion partner cleaved by hydrolysis of a peptide bond by chymosin shown in Table 2 with each of the modified prodomains surveyed relative to yields attained with an unmodified chymosin prodomain, meeting limitations of claims 46 and 47 herein. See further the paragraphs 0011-0018, 0055-0071, and 0089-0156 wherein the use of the prodomain as a separable component for purification of a desired fusion partner in affinity chromatography is disclosed and the use of various host cells are disclosed for the recombinant production of fusion polypeptides of Van Rooijen et al., including several of the host cells recited in claim 17 herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 USC § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 7, 8, 11, 12, 13, 14, 17, and 48 are rejected under 35 USC § 103(a) as being unpatentable over Van Rooijen et al. as applied to claims 1, 46, and 47 above, in view of Grøn et al., 1996, made of record herewith. The teachings of Van Rooijen et al. of modification of a chymosin prodomain, discussed above, are taken as before. Grøn et al. teach the improvement of the affinity of a subtilisin having an amino acid sequence modification within the protease subsite that accepts the S4 amino acid of the prodomain's carboxyl terminal region for several modified peptide substrates representing the P4-P3-P2-P1 tetrapeptide of the "corresponding" unmodified subtilase wherein phenylalanine is maintained at the P1 position of the prodomain and is not altered, wherein proline and glycine are maintained at, respectively, the P2 and P3 positions of the prodomain, and wherein the P4 position is modified by introducing several charged, or hydrophobic, or hydrophilic amino acids and the binding affinity, measured by rate

of proteolysis, is determined for each. See results in Table 3 at page 110. Having previously determined that phenylalanine was the most favorable resident at both the P1 and P4 positions of the prodomain promoting cleavage by the native subtilisin, see results in Table 2 at page 108, and the accompanying discussion at pages 10 7 and 109, Grøn et al. teach that the nature of the substituent at a position in the S4 subsite of the protease can determine the affinity for, and overall efficiency of hydrolysis of, a modified P4-P1 region for any particular modification of the protease. See, e.g., the marked increase in catalytic rate where negatively-charged aspartate resides in the S4 subsite of the modified protease and positively charged arginine resides at the S4 position of the substrate as well as the marked increase in catalytic rate where the small amino acid valine resides in the S4 subsite of the modified protease and the bulky, hydrophobic, phenylalanine resides at the S4 position of the substrate, even with respect to the residence of the native valine in the S4 subsite of the unmodified protease. Grøn et al. further teach the evaluation of binding affinities, as evidenced by rates of hydrolysis of substrate, for the different modifications of the protease subsite and the various P4 resident amino acids in Figures 1 and 2 at page 111, demonstrating that the state of the art and the level of skill in the art at the time the invention was made supported the similar evaluations of contributions to affinity of binding and rate of hydrolysis of any amino acids resident at each of the P4 through P1 positions of a subtilisin prodomain, individually or collectively, for any corresponding native subtilisin or a variant of the native subtilisin having, at least, modifications in one or more of the S1 through S4 subsite regions therein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Grøn et al. to the modification of the amino acid sequence region comprising one or more of the P4 through P1 positions of a subtilisin prodomain by preparing polynucleotides encoding a fusion polypeptide comprising a modified subtilisin prodomain and, at least, a hormone fusion partner of claim 11 herein, wherein the modified prodomains have enhanced affinity for binding to, and hydrolytic cleavage by, either a native subtilisin or modified subtilisin, wherein the modification may be in any of the S1, S2, S3, or S4 subsites, and to substitute the modified subtilisin prodomain for the modified chymosin domain, as well as replacing chymosin with a "corresponding" subtilisin, in the fusion polypeptides and methods of Van Rooijen et al. in order to practice the methods of purification of Van Rooijen et al. according to claims 2, 3, 5, 7, 8, 11, 12, 13, 14, and 48 herein. It would also have been obvious to such an artisan to express polynucleotides encoding fusion polypeptides comprising modified subtilisin prodomains and a desired fusion partner, such as a hormone, using a host cell of Van Rooijen et al. which is also a host cell according to claim 17 herein.

This is (i) because the prior art made of record herein, both in the communication mailed 23 November 2007 and in the PTO-Form 892 accompanying this communication, are evidence of the widespread modification of, and use of modified subtilisins, including those with modified subsites that bind one or more of the P4 – P1 amino acids at the carboxyl terminus of a subtilisin prodomain, in the prior art, (ii) because Van Rooijen et al. teach that it is advantageous to use protease prodomains comprising carboxyl terminus modifications as amino-proximal fusion partners in recombinant production, and subsequent purification of, desired commercially or medically important carboxyl proximal fusion partners, and (iii) because Grøn et al. demonstrate that optimizing the binding affinity of, and hydrolytic processing of, the region of the P4 – P1 amino acids present at the carboxyl terminus of any subtilisin prodomain for a particular native or modified subtilisin was well within the state of the art and level of skill in the art at the time the invention was made. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 4, 6, 15, and 16 are rejected under 35 USC § 103(a) as being obvious over as Van Rooijen et al. and Grøn et al., 1996, as applied to, at least, claims 1-3 and 5 above, in view of Grøn et al., 1992, made of record herewith. The teachings of Van Rooijen et al. and Grøn et al., 1996, discussed above, are taken as before. Grøn et al., 1992, teach that two commercially prominent subtilisins, BPN' and Savinase, share a highest binding affinity for phenylalanine at their S4 binding subsites, have broad specificity for any amino acid at their S3 binding subsites with preference for a positively-charged amino acid, share a highest binding affinity for alanine at their S2 subsites, and share highest binding affinities for both phenylalanine and leucine at their S4 subsites (the order is reversed between the two subtilisins). See Tables II and III and accompanying discussion spanning pages 6014-6016. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a modified subtilisin prodomain according to claims 4 and 6 and, at least, the FKAF modified prodomain of claim 15 as an amino-proximal component of a fusion polypeptide comprising a carboxyl-proximal fusion partner of claim 16, e.g., a hormone of Van Rooijen et al., by preparing polynucleotides encoding a fusion polypeptide comprising a modified subtilisin prodomain wherein the modified prodomains have enhanced affinity for binding to, and hydrolytic cleavage by, either a native subtilisin or modified subtilisin, and wherein the modifications comprise a phenylalanine at the P4 position, a charged amino acid, such as lysine, at the P3 position, an alanine at the P2 position and either a phenylalanine and leucine at the P1 position because Grøn et al. 1992 teach that these are the kinds of amino acids having the highest binding affinities for the

corresponding S1 through S4 subsites of the two most commonly used subtilisins in the prior art. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

While rejected above for indefinite description under 35 U.S.C. § 112, second paragraph, the subject matter of a modified subtilisin prodomain of claim 9 herein having both a lysine at the P3 position and a methionine at the P4 position and the carboxyl-terminal nonapeptide of claim 10 herein having any of the six modifications represented by its nonapeptide formula are free of the prior art of record herein. This is because neither Grøn et al. 1996 nor Grøn et al. 1992 suggest that methionine might be a suitable substituent at the P4 position of a subtilisin prodomain and because the prior art neither discloses or suggests the presence, or introduction, of a lysine at the P6 position and a leucine at the P5 position of a subtilisin prodomain.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashaat T. Nashed/
Nashaat T. Nashed, Ph.D.
Supervisory Primary Examiner
Art Unit 1652

William W. Moore
24 April 2008